

SUBSTITUTED IMIDAZOLES USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASES

FIELD OF THE INVENTION

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This invention relates to a series of substituted imidazoles, pharmaceutical compositions containing them and intermediates used in their manufacture. The compounds of the invention inhibit the production of a number of inflammatory cytokines, particularly, TNF- α , and IL-1 β . Compounds of this invention are useful in the treatment of diseases associated with the overproduction of inflammatory cytokines.

BACKGROUND OF THE INVENTION

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The inflammatory cytokines, IL-1 β and TNF- α play an important role in a number of inflammatory diseases such as rheumatoid arthritis. C. Dinarello et al., Inflammatory cytokines: Interleukin-1 and Tumor Necrosis Factor as Effector Molecules in Autoimmune Diseases *Curr. Opin. Immunol.* **1991**, 3, 941-48. Arthritis is an inflammatory disease which affects millions of people and can strike at any joint of the human body. Its symptoms range from mild pain and inflammation in affected joints, to severe and debilitating pain and inflammation. Although the disease is associated mainly with aging adults, it is not restricted to adults. The most common arthritis therapy involves the use of nonsteroidal antiinflammatory drugs (NSAID) to alleviate the symptoms.

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However, despite their widespread use, many individuals cannot tolerate the doses necessary to treat the disease over a prolonged period of time. In addition, NSAIDs merely treat the symptoms of disease without affecting the underlying cause. Other drugs, such as methotrexate, gold salts, D-penicillamine, and prednisone are often used when patients fail to respond to NSAIDs. These drugs also have significant toxicities and their mechanism of action remain unknown.

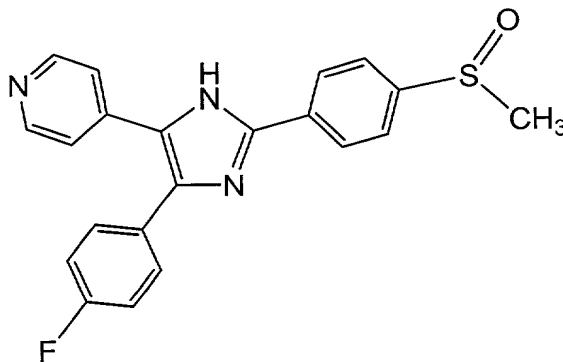
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Receptor antagonists to IL-1 β and monoclonal antibodies to TNF- α have

been shown to reduce symptoms of rheumatoid arthritis in small-scale human clinical trials. In addition to protein based therapies, there are small molecule agents which inhibit the production of these cytokines and have demonstrated activity in animal arthritis models. J.C. Boehm et al., 1-Substituted 4-Aryl-5-pyridinylimidazoles: A New Class of Cytokine Suppressive Drugs With Low 5-Lipoxygenase and Cyclooxygenase Inhibitory Potency, *J. Med. Chem.*, **1996**, 39, 3929-37. Of these small molecule agents, SB 203580 has proved effective in reducing the production of TNF- α and IL-1 in LPS stimulated human monocyte cell lines with IC₅₀ values of 50 to 100 nM. J. Adams et al., Imidazole Derivatives And Their Use as Cytokine Inhibitor, International Patent application WO 93/14081, July 23, 1993. In addition to this in vitro test, SB 203580 inhibits the production of the inflammatory cytokines in rats and mice at IC₅₀ values of 15 to 25 mg/kg. A.M. Badger, et al, Pharmacological Profile of SB 203580, A Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function, *The Journal of Pharmacology and Experimental Therapeutics*, **1996**, 279, 1453-61. Although human data is currently unavailable for SB 203580, monoclonal antibodies to TNF- α have proved efficacious in the treatment of rheumatoid arthritis. M.J. Elliot et al., Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α , *Arthritis Rheum.* 1993 36, 1681-90. Due to SB 203580's oral activity and potency in animal models, researchers have suggested that a compound with this profile has potential as a viable treatment for rheumatoid arthritis. A.M. Badger, et al. Pharmacological Profile of SB 203580, A Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function, *The Journal of Pharmacology and Experimental Therapeutics*, **1996**, 279, 1453-61.

SB 203580 and other small molecule agents reduce the production of inflammatory cytokines by inhibiting the activity of a serine/threonine kinase p38 (note other researchers refer to this enzyme as CSBP), at an IC₅₀ of 200 nM. D. Griswold et al., Pharmacology of Cytokine Suppressive Anti-inflammatory Drug Binding Protein (CSPB), A Novel Stress-Induced Kinase, *Pharmacology*

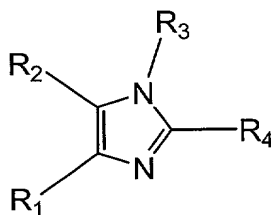
Communications, **1996**, 7, 323-29. Although the precise mechanism of this kinase is unknown, it has been implicated in both the production of TNF- α and the signaling responses associated with the TNF- α receptor.



SB 203580

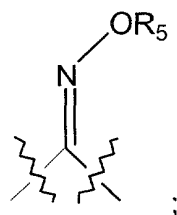
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United States Patents 5,965,583 (hereby incorporated by reference) describes substituted imidazoles of the formula:



wherein R₁ is phenyl, substituted phenyl (where the substituents are selected from the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile), or heteroaryl where the heteroaryl contains 5 to 6 ring atoms; R₂ is phenyl, substituted phenyl (where the substituents are selected from the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile), heteroaryl where the heteroaryl contains 5 to 6 ring atoms and is optionally C₁₋₅alkyl substituted; R₃ is hydrogen, SEM, C₁₋₅alkoxycarbonyl, aryloxycarbonyl, arylC₁₋₅alkyloxycarbonyl, arylC₁₋₅alkyl, substituted arylC₁₋₅alkyl (where the aryl substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl, C₁₋₅alkoxy, halogen, amino, C₁₋₅alkylamino, and diC₁₋₅alkylamino), phthalimidoC₁₋₅alkyl, aminoC₁₋₅alkyl, diaminoC₁₋₅alkyl,

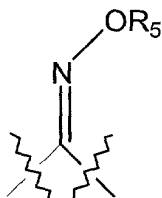
succinimidoC₁₋₅alkyl, C₁₋₅alkylcarbonyl, arylcarbonyl, C₁₋₅alkylcarbonylC₁₋₅alkyl, aryloxy carbonylC₁₋₅alkyl, heteroarylC₁₋₅alkyl where the heteroaryl contains 5 to 6 ring atoms; R₄ is -A-(CH₂)_q-X wherein A is vinylene, ethynylene or



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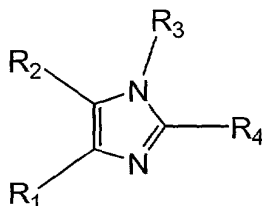
where R₅ is selected from the group consisting of hydrogen, C₁₋₅alkyl, phenyl and phenylC₁₋₅alkyl; q is 0-9; X is selected from the group consisting of hydrogen, hydroxy, vinyl, substituted vinyl (where one or more substituents are selected from the group consisting of fluorine, bromine, chlorine and iodine), ethynyl, substituted ethynyl (where the substituents are selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine), C₁₋₅alkyl, substituted C₁₋₅alkyl (where the alkyl substituents are selected from the group consisting of one or more C₁₋₅alkoxy, trihaloalkyl, phthalimido and amino), C₃₋₇cycloalkyl, C₁₋₅alkoxy, substituted C₁₋₅alkoxy (where the alkyl substituents are selected from the group consisting of phthalimido and amino), phthalimidooxy, phenoxy, substituted phenoxy (where the phenyl substituents are selected from the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy), phenyl, substituted phenyl (where the phenyl substituents are selected from the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy), arylC₁₋₅alkyl, substituted arylC₁₋₅alkyl (where the aryl substituents are selected from the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy), amino, C₁₋₅alkylamino, diC₁₋₅alkylamino, nitrile, oxime, benzyloxyimino, C₁₋₅alkyloxyimino, phthalimido, succinimido, C₁₋₅alkylcarbonyloxy, phenylcarbonyloxy, substituted phenylcarbonyloxy (where the phenyl substituents are selected from the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy), phenylC₁₋₅alkylcarbonyloxy (where the phenyl substituents are selected from the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy), aminocarbonyloxy, C₁₋₅alkylaminocarbonyloxy, diC₁₋₅alkylaminocarbonyloxy, C₁₋₅alkoxycarbonyloxy, substituted C₁₋₅alkoxycarbonyloxy (where the alkyl substituents are selected from the group consisting of methyl, ethyl, isopropyl and hexyl), phenoxycarbonyloxy,

- substituted phenoxy carbonyloxy (where the phenyl substituents are selected from the group consisting of C₁₋₅alkyl, C₁₋₅alkoxy and halogen), C₁₋₅alkylthio, substituted C₁₋₅alkylthio (where the alkyl substituents are selected from the group consisting of hydroxy and phthalimido), C₁₋₅alkylsulfonyl, phenylsulfonyl, 5 substituted phenylsulfonyl (where the phenyl substituents are selected from the group consisting of bromine, fluorine, chlorine, C₁₋₅alkoxy and trifluoromethyl); with the proviso: if A is



- 10 q is 0 and X is H, R₃ may not be SEM; and pharmaceutically acceptable salts thereof as useful in the treatment of diseases associated with the overproduction of inflammatory cytokines.

United States Patent 6,040,320 (hereby incorporated by reference) also describes substituted imidazoles of the formula:



wherein R₁ is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or substituted phenyl wherein the substituents are independently selected from one or members of the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile; R₂ is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, substituted heteroaryl wherein the substituents are independently selected from one or more members of the group consisting of C₁₋₅alkyl and halogen, or substituted phenyl wherein the substituents are independently selected from one or members of the group consisting of

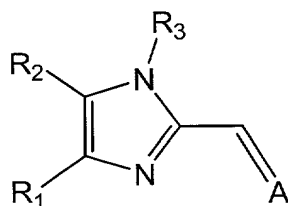
C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile; R_3 is hydrogen, SEM, C_{1-5} alkoxycarbonyl, aryloxy carbonyl, aryl C_{1-5} alkyloxy carbonyl, aryl C_{1-5} alkyl, phthalimido C_{1-5} alkyl, amino C_{1-5} alkyl, diamino C_{1-5} alkyl, succinimido C_{1-5} alkyl, C_{1-5} alkylcarbonyl, arylcarbonyl, C_{1-5} alkylcarbonyl C_{1-5} alkyl, aryloxy carbonyl C_{1-5} alkyl, heteroaryl C_{1-5} alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted aryl C_{1-5} alkyl wherein the aryl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, C_{1-5} alkoxy, halogen, amino, C_{1-5} alkylamino, and di C_{1-5} alkylamino; R_4 is $(A)_n-(CH_2)_q-X$ wherein A is sulfur or carbonyl; n is 0 or 1; q is 0-9; X is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{1-5} alkoxy, phenoxy, phenyl, aryl C_{1-5} alkyl, amino, C_{1-5} alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, phenylsulfonyl, substituted sulfonamido wherein the sulfonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, aryl C_{1-5} alkyl, thienyl, furanyl, and naphthyl; substituted vinyl wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine, substituted ethynyl wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine, substituted C_{1-5} alkyl wherein the substituents are selected from the group consisting of one or more C_{1-5} alkoxy, trihaloalkyl, phthalimido and amino, substituted phenyl wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy, substituted phenoxy wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy, substituted C_{1-5} alkoxy wherein the alkyl substituent is selected from the group consisting of phthalimido and amino, substituted aryl C_{1-5} alkyl wherein the alkyl substituent is hydroxyl, substituted aryl C_{1-5} alkyl wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy, substituted amido wherein the carbonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, aryl C_{1-5} alkyl, thienyl, furanyl, and naphthyl, substituted phenylcarbonyl wherein

the phenyl substituents are independently selected from one or members of the group consisting of C₁₋₅alkyl, halogen and C₁₋₅alkoxy, substituted C₁₋₅alkylthio wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido, substituted C₁₋₅alkylsulfonyl wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido, substituted phenylsulfonyl wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C₁₋₅alkoxy and trifluoromethyl, with the proviso: if A is sulfur and X is other than hydrogen, C₁₋₅alkylaminocarbonyl, phenylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl, C₁₋₅alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1; if A is sulfur and q is 1, then X cannot be C₁₋₂alkyl; if A is carbonyl and q is 0, then X cannot be vinyl, ethynyl, C₁₋₅alkylaminocarbonyl, phenylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl, C₁₋₅alkylsulfonyl or phenylsulfonyl; if A is carbonyl, q is 0 and X is H, then R₃ is not SEM; if n is 0 and q is 0, then X cannot be hydrogen; and pharmaceutically acceptable salts thereof as useful in the treatment of diseases associated with the overproduction of inflammatory cytokines.

The object of the present invention is to provide a series of substituted imidazoles, pharmaceutical compositions containing them and intermediates used in their manufacture. Another object is to provide a method for treating diseases associated with the overproduction of inflammatory cytokines.

SUMMARY OF THE INVENTION

The invention relates to compounds of Formula I:



Formula I

wherein:

R₁ is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms);

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R₂ is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₅alkyl and halogen);

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R₃ is selected from the group consisting of hydrogen, C₁₋₅alkyl, arylC₁₋₅alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₅alkyl, C₁₋₅alkoxy, halogen and amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl)), heteroarylC₁₋₅alkyl (wherein heteroaryl contains 5 to 6 ring atoms), aminoC₁₋₅alkyl, diaminoC₁₋₅alkyl, phthalimidoC₁₋₅alkyl, succinimidoC₁₋₅alkyl, SEM, C₁₋₅alkylcarbonyl, C₁₋₅alkylcarbonylC₁₋₅alkyl, C₁₋₅alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, arylC₁₋₅alkyloxycarbonyl and aryloxycarbonylC₁₋₅alkyl;

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A is a five to seven member heterocyclcyl ring optionally substituted with one to two substituents independently selected from X; wherein the ring has an unsaturated bond of attachment at a ring carbon atom; has a ring nitrogen atom substituted with a substituent selected from W adjacent to the ring carbon of attachment; has a ring carbon atom adjacent to the ring carbon of attachment; optionally has 1 or 2 double bonds formed in the ring between adjacent ring members; and, optionally has 1 or 2 ring members independently selected from the group consisting of O, N and S;

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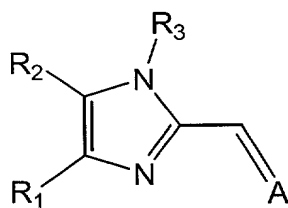
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W is a substituent selected from the group consisting of hydrogen, C₁₋₅alkyl,

- 5 C₁₋₅alkoxy, aminoC₁₋₅alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl), arylC₁₋₅alkyl and heteroarylC₁₋₅alkyl (wherein the aryl, heteroaryl and C₁₋₅alkyl portions of any of the foregoing substituents are optionally substituted with one to three substituents independently selected from the group consisting of halogen, C₁₋₅alkyl, C₁₋₅alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl) and nitrile); and,
- 10 X is a substituent selected from the group consisting of C₁₋₅alkyl, C₁₋₅alkenyl, C₁₋₅alkynyl, C₁₋₅alkoxy, amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl), aminoC₁₋₅alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl), aryl, arylC₁₋₅alkyl, heteroaryl and heteroarylC₁₋₅alkyl (wherein the aryl, heteroaryl and C₁₋₅alkyl portions of any of the foregoing substituents are optionally substituted with one to two substituents independently selected from the group consisting of halogen, C₁₋₅alkyl, C₁₋₅alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl) and nitrile);
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and pharmaceutically acceptable salts thereof.

- 25 The present invention includes a method for preparing a compound of Formula I:



Formula I

wherein

R₁ is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of

C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms);

5 R₂ is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₅alkyl and halogen);

10 R₃ is selected from the group consisting of hydrogen, C₁₋₅alkyl, arylC₁₋₅alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₅alkyl, C₁₋₅alkoxy, halogen and amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl)), heteroarylC₁₋₅alkyl (wherein heteroaryl contains 5 to 6 ring atoms), aminoC₁₋₅alkyl, diaminoC₁₋₅alkyl, phthalimidoC₁₋₅alkyl, succinimidoC₁₋₅alkyl, SEM, C₁₋₅alkylcarbonyl, C₁₋₅alkylcarbonylC₁₋₅alkyl, C₁₋₅alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, arylC₁₋₅alkyloxycarbonyl and
20 aryloxycarbonylC₁₋₅alkyl;

A is a five to seven member heterocyclyl ring optionally substituted with one to two substituents independently selected from X; wherein the ring has an unsaturated bond of attachment at a ring carbon atom; has a ring nitrogen atom substituted with a substituent selected from W adjacent to the ring carbon of attachment; has a ring carbon atom adjacent to the ring carbon of attachment; optionally has 1 or 2 double bonds formed in the ring between adjacent ring members; and, optionally has 1 or 2 ring members independently selected from the group consisting of O, N and S;

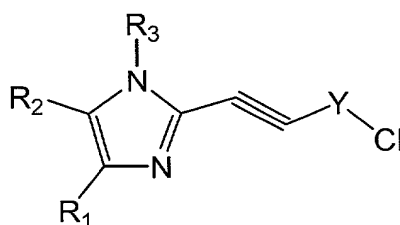
30 W is a substituent selected from the group consisting of hydrogen, C₁₋₅alkyl, C₁₋₅alkoxy, aminoC₁₋₅alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl), arylC₁₋₅alkyl and

heteroarylC₁₋₅alkyl (wherein the aryl, heteroaryl and C₁₋₅alkyl portions of any of the foregoing substituents are optionally substituted with one to three substituents independently selected from the group consisting of halogen, C₁₋₅alkyl, C₁₋₅alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl) and nitrile); and,

X is a substituent selected from the group consisting of C₁₋₅alkyl, C₁₋₅alkenyl, C₁₋₅alkynyl, C₁₋₅alkoxy, amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl), aminoC₁₋₅alkyl (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl), aryl, arylC₁₋₅alkyl, heteroaryl and heteroarylC₁₋₅alkyl (wherein the aryl, heteroaryl and C₁₋₅alkyl portions of any of the foregoing substituents are optionally substituted with one to two substituents independently selected from the group consisting of halogen, C₁₋₅alkyl, C₁₋₅alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl) and nitrile);

and pharmaceutically acceptable salts thereof; comprising,

converting an intermediate compound of Formula II



Formula II

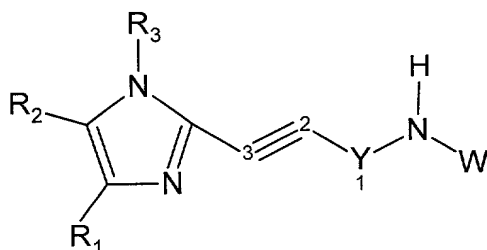
wherein

Y is a three to five member linear alkylene, alkenylene, heteroalkylene or heteroalkenylene chain optionally substituted with one to two substituents independently selected from X; wherein the alkenylene and heteroalkenylene chain has 1 or 2 double bonds formed in the chain

between adjacent members; and, wherein the heteroalkylene and heteroalkenylene chain has 1 or 2 members independently selected from the group consisting of O, N and S; and,

- 5 all other substituents are as previously defined;

by ammonolysis, using an excess of a compound selected from $H_2N(W)$ in an appropriate solvent, to form a secondary amine intermediate of Formula III; and,

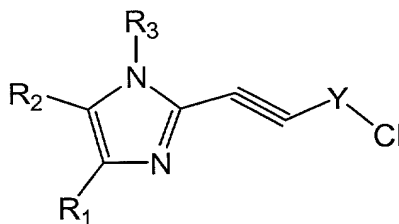


Formula III

- 10 coupling the amine at the 2 position of the triple bond by a Michael addition, in the presence of appropriate reagents and solvents, to form the compound of Formula I.

The present invention also includes an intermediate compound of

- 15 Formula II:



Formula II

wherein

- R_1 is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms);
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5 R₂ is selected from the group consisting of phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C₁₋₅alkyl, halogen, nitro, trifluoromethyl and nitrile) and heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₅alkyl and halogen);

10 R₃ is selected from the group consisting of hydrogen, C₁₋₅alkyl, arylC₁₋₅alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₅alkyl, C₁₋₅alkoxy, halogen and amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl)), heteroarylC₁₋₅alkyl (wherein heteroaryl contains 5 to 6 ring atoms), aminoC₁₋₅alkyl, diaminoC₁₋₅alkyl, phthalimidoC₁₋₅alkyl, succinimidoC₁₋₅alkyl, SEM, 15 C₁₋₅alkylcarbonyl, C₁₋₅alkylcarbonylC₁₋₅alkyl, C₁₋₅alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, arylC₁₋₅alkyloxycarbonyl and aryloxycarbonylC₁₋₅alkyl; and,

20 Y is a three to five member linear alkylene, alkenylene, heteroalkylene or heteroalkenylene chain optionally substituted with one to two substituents independently selected from X; wherein the alkenylene and heteroalkenylene chain has 1 or 2 double bonds formed in the chain between adjacent members; and, wherein the heteroalkylene and heteroalkenylene chain has 1 or 2 members independently selected from 25 the group consisting of O, N and S;

with the proviso that Y cannot be selected from (CH₂)₃;

and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are useful as inhibitors of

TNF- α and IL-1. Some of the instant compounds are more active than others and, thereby, have a structure activity relationship that may be preferred, more preferred or most preferred.

5 Compounds of Formula I that are preferred include a compound wherein:

R_1 is phenyl (optionally substituted with one to five substituents independently selected from the group consisting of C_{1-5} alkyl and halogen);

10 more preferably, R_1 is phenyl substituted with a substituent selected from halogen;

and, most preferably, R_1 is phenyl substituted with fluorine.

15 Other compounds of Formula I that are preferred include a compound wherein:

R_2 is heteroaryl (wherein heteroaryl contains 5 to 6 ring atoms and is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5} alkyl and halogen);

20 more preferably, R_2 is selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 4-pyrrolinyl, 5-pyrrolinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-imidazoliny, 4-imidazoliny, 5-imidazoliny, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-pyrazoliny, 4-pyrazoliny, 5-pyrazoliny, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 4-1,2,3-oxadiazolyl, 5-1,2,3-oxadiazolyl, 4-1,2,3-triazolyl, 5-1,2,3-triazolyl, 2-1,3,4-thiadiazolyl, 5-1,3,4-thiadiazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 30 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl and 2-1,3,5-triazinyl optionally substituted with one substituent selected from C_{1-5} alkyl; and,

most preferably, R_2 is selected from the group consisting of 4-pyridinyl, 4-pyrimidinyl and (2-butyl)pyridin-4-yl.

Embodiments of compounds of Formula I that are preferred also include
5 a compound wherein:

R_3 is selected from the group consisting of hydrogen, C_{1-5} alkyl and aryl C_{1-5} alkyl (wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-5} alkyl, C_{1-5} alkoxy, halogen and amino (wherein amino is optionally substituted with one to two
10 substituents independently selected from C_{1-5} alkyl));

more preferably, R_3 is selected from the group consisting of hydrogen and phenyl C_{1-5} alkyl (wherein phenyl is optionally substituted with one substituent selected from C_{1-5} alkoxy); and,
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most preferably, R_3 is selected from the group consisting of benzyl, phenethyl and phenylpropyl.

Other preferred embodiments of compounds of Formula I include a
20 compound wherein:

A is selected from the group consisting of pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, hexahydro-1*H*-azepine, hexahydro-1*H*-1,3-diazepine, hexahydro-1,3-oxazepine, hexahydro-1,3-thiazepine and hexahydro-1*H*-1,3,5-triazepine;
25 and,

more preferably, A is selected from the group consisting of pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl and piperazinyl.

30 Additional compounds of Formula I that are preferred include a compound wherein:

W is a substituent selected from the group consisting of hydrogen, C_{1-5} alkyl and C_{1-5} alkoxy (wherein C_{1-5} alkyl for any of the foregoing substituents is

optionally substituted with one to three substituents independently selected from the group consisting of halogen, C₁₋₅alkyl, C₁₋₅alkoxy, aryl, heteroaryl, amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl) and nitrile);

5

more preferably, W is a substituent selected from the group consisting of hydrogen and C₁₋₅alkyl; and,

10

most preferably, W is a substituent selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl and *t*-butyl.

Preferred embodiments of compounds of Formula I also include a compound wherein:

15

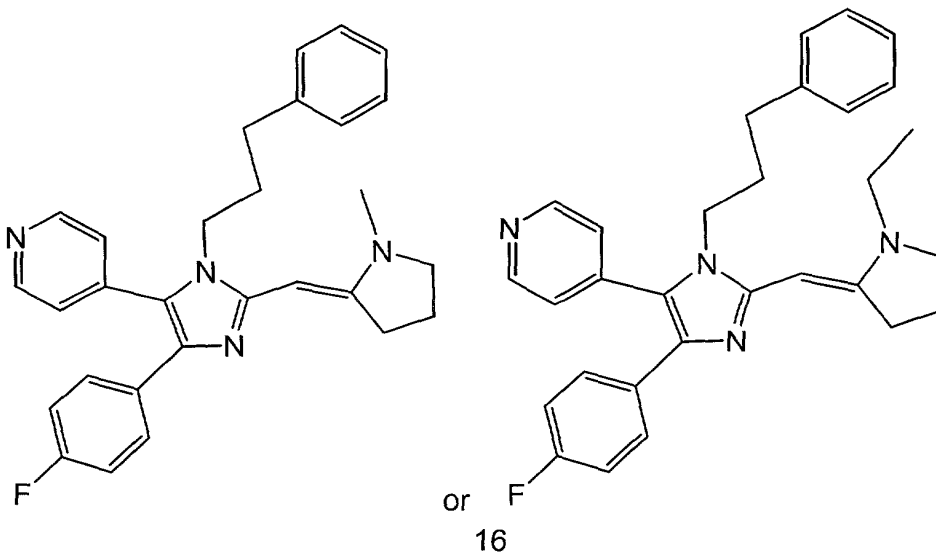
X is a substituent selected from the group consisting of C₁₋₅alkyl, C₁₋₅alkenyl, C₁₋₅alkynyl, C₁₋₅alkoxy and amino (wherein amino is optionally substituted with one to two substituents independently selected from C₁₋₅alkyl);

more preferably, X is a substituent selected from C₁₋₅alkyl; and,

20

most preferably, X is a substituent selected from the group consisting of methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl and *t*-butyl.

The preferred compounds of Formula I include a compound of formula:



and pharmaceutically acceptable salts thereof.

5 In a preferred embodiment of the method of the present invention, Y is a three to five member linear alkylene chain optionally substituted with one to two substituents independently selected from X. In a more preferred embodiment of the instant method, Y is an unsubstituted three to five member linear alkylene chain.

10 In a preferred embodiment of the intermediate compound of Formula II, Y is a four to five member linear alkylene chain optionally substituted with one to two substituents independently selected from X. In a more preferred embodiment of the instant compound, Y is an unsubstituted four to five member linear alkylene chain.

15 The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are defined. The term "independently" means that when there are more than one substituent, the substituents may be different.

20 The term "alkyl" refers to straight and branched-chain alkyl groups; "alkoxy" refers O-alkyl where alkyl is as defined supra. The term cycloalkyl refers to a cyclic alkyl ring of five to seven carbon atom members. Examples of such cyclic alkyl rings include pentyl, hexyl or heptyl.

25 In the present invention, the term heterocyclyl refers to the "A" substituent which comprises a cyclic alkyl ring of five to seven members wherein at least one member is a first nitrogen atom substituted with a substituent selected from W.

30 The heterocyclyl ring may contain up to two heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. Up to two carbon atom ring members may be optionally substituted with one to two

substituents selected from X or may have empty valences satisfied by the ring itself. Nitrogen atom ring members in addition to the first nitrogen atom ring member may be substituted with one substituent selected from W or may have empty valences satisfied by the ring itself.

5

In the compounds of the present invention, the "A" substituent heterocyclyl ring is attached to the 2 position of the imidazole scaffold via a ring carbon atom and a linking carbon atom. The ring carbon atom forms a double bond with the linking carbon atom. The heterocyclyl ring contains at least a
10 single nitrogen heteroatom substituted with a substituent selected from W. The single nitrogen atom will be adjacent to the ring carbon atom of attachment. The ring carbon of attachment will also have an adjacent ring carbon.

For instant compounds of the invention, the carbon atom ring members
15 that form the heterocyclyl ring "A" substituent are fully saturated except for the single carbon of attachment. Other compounds of the invention may have a partially unsaturated heterocyclyl ring that forms the "A" substituent. Preferred partially unsaturated heterocyclyl rings may contain one or two double bonds. Such compounds are not considered to be fully aromatic and are not referred
20 to as heteroaryl compounds. Therefore, a five member heterocyclyl ring that forms the "A" substituent may optionally have a double bond formed in the ring between adjacent ring members; a six or seven member heterocyclyl ring that forms the "A" substituent may have two double bonds formed in the ring between adjacent ring members. The carbon ring member of attachment may
25 stably form only a single bond with an adjacent carbon ring member and the first nitrogen ring member. The first nitrogen ring member substituted with a substituent selected from W links the carbon ring member of attachment to another ring member (which may be a carbon or a second nitrogen atom) and may stably form only a single bond with both ring members.

30

The term "alkylene" refers to a straight chain alkyl linking group. The term "alkylene" refers to a straight chain alkenyl linking group wherein one or two double bonds are formed in the chain between adjacent members. The

term "heteroalkylene" refers to a straight chain alkyl linking group wherein at least one member is a heteroatom independently selected from the group consisting of nitrogen, oxygen and sulfur. The heteroalkylene chain may contain up to two heteroatoms. Similarly, the term "heteroalkenylene" refers to a straight chain alkenyl linking group wherein one or two double bonds are formed in the chain between adjacent chain members.

In particular, the "Y" substituent comprises a three to five member alkylene, alkenylene, heteroalkylene or heteroalkenylene chain optionally substituted with one to two substituents independently selected from X. Up to two carbon atom chain members may be optionally substituted with one to two substituents selected from X or may have empty valences satisfied by the ring itself. A nitrogen heteroatom chain member may be optionally substituted with one substituent selected from W or may have empty valences satisfied by the ring itself.

In the compounds of the present invention, the "Y" substituent is attached to an adjacent unsaturated carbon atom. The terminal atom of the "Y" substituent attached to the adjacent carbon atom is either a carbon atom or a heteroatom that forms a stable chemical bond within the "A" substituent heterocyclyl ring. The adjacent carbon atom forms a triple bond with a linking carbon atom whereby the "Y" substituent is attached to the 2 position of the imidazole scaffold. For instant compounds of the invention, the "Y" substituent is a fully saturated alkylene or heteroalkylene chain. Other compounds of the invention may have a partially unsaturated alkenylene or heteroalkenylene chain that forms the "Y" substituent. Preferred unsaturated chains may contain one or two double bonds.

The term aryl refers to a single aromatic ring of six carbon members or a bicyclic aromatic ring of ten carbon members. Examples of such aryl rings include phenyl and naphthyl.

The term heteroaryl refers to an aromatic ring of five or six members

wherein the ring has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen or sulfur. In the case of five-membered rings, the heteroaryl ring contains one member of nitrogen, oxygen or sulfur and, in addition, may contain up to two additional nitrogens. In the case of six-membered rings, the heteroaryl ring may contain from one to three nitrogen atoms. For the case wherein the six member ring has three nitrogens, at most two nitrogen atoms are adjacent.

In the present invention, the term "Michael addition" refers to the nucleophilic addition of a carbanion (such as the nitrogen portion of $-N(H)(W)$ in a compound of Formula IV) to the β position of an α,β -unsaturated carbon-carbon bond (such as the 2 position of the triple bond portion of a compound of Formula IV), a process known to those skilled in the art.

As used in this invention the term "cytokine" refers to the proteins $TNF-\alpha$ and $IL-1\beta$. Cytokine related disorders are diseases of humans and other mammals where the overproduction of cytokines causes the symptoms of the disease. The overproduction of the cytokines, $TNF-\alpha$ and $IL-1\beta$ has been linked to a number of diseases including, but not limited to, rheumatoid arthritis, inflammatory bowel disease, septic shock osteoporosis, osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin dependent diabetes, periodontal disease, restenosis, alopecia areata, T-cell depletion in HIV infection or AIDS, psoriasis, acute pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, multiple sclerosis, cachexia, Alzheimer's disease, stroke, Crohn's disease, inflammatory bowel disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus.

The term "effective dose" refers to an amount of a compound of Formula I which reduces the amount of $TNF\alpha$ and/or $IL-1\beta$ which may be detected in a mammal suffering from a cytokine mediated disorder. In addition, the term "effective dose" refers to an amount of a compound of Formula I which reduces

the symptoms of a cytokine related disorder.

The term "FCS" represents fetal calf serum, "TCA" represents trichloroacetic acid and the "RPMI" represents the medium from the Roswell
 5 Park Memoria Inst. (Sigma cat # R0833). "SEM" refers to 2-(trimethylsilyl)ethoxymethyl) and "LDA" refers to lithium diisopropylamide. The symbol "Ph" refers to phenyl and "PHT" refers to phthalimido.

The compounds of the present invention may be prepared by the
 10 following scheme, which may produce more than one embodiment of the instant compounds. Such embodiments are intended to be included within the scope of this invention. United States Patent 5,965,583 (heretofore incorporated by reference) and U.S. Patent 6,040,320 (heretofore incorporated by reference) disclose schemes and procedures which may be used to prepare
 15 intermediates for use in the present invention. Compounds prepared from such intermediates are intended to be within the scope of this invention.

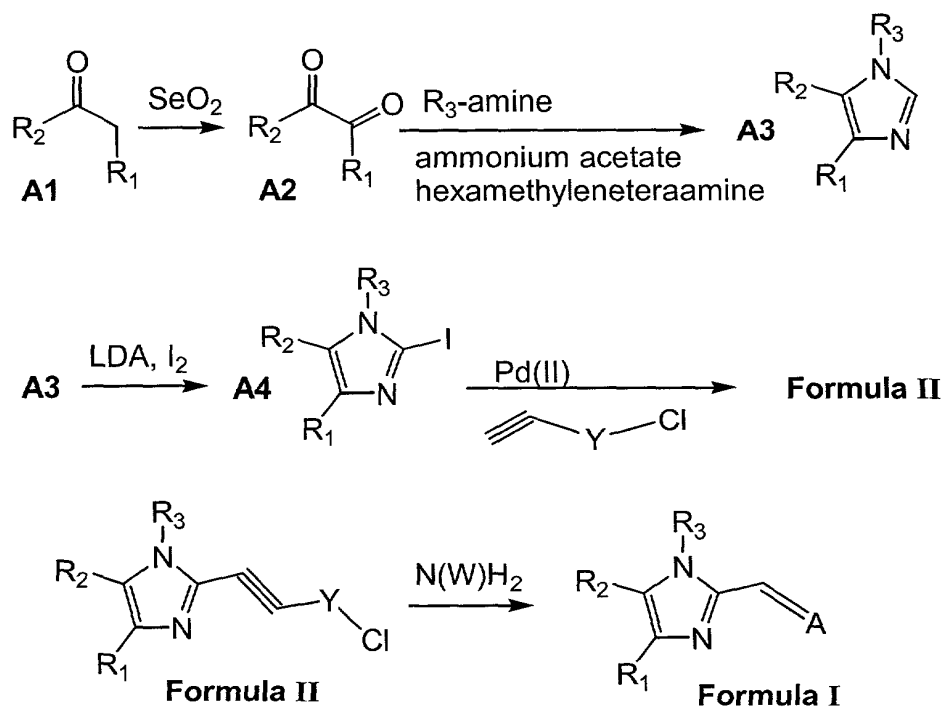
The compounds of the invention may be prepared as shown in Scheme
 A. Compound **A1** to the Compound of **Formula II** depicted in Scheme **A** were
 20 produced according to the procedure described for Example 14 in United States Patents 5,965,583. Other imidazoles, which may be prepared using the methods of the present invention, unsubstituted at the 1-position are subject to tautomerization; therefore, substituents for R₁ and R₂ may be interchangeable when R₃ is hydrogen.

25 Intermediate Compound **A1** was synthesized according to the methodology of Lantos et. al. *J. Org. Chem.* **1988**, 53, 4223-4227. Compound **A1** was reacted with selenium dioxide (SeO₂) in dioxane at about 80 °C and afforded diketone Compound **A2**. Treatment of Compound **A2** with
 30 phenylpropylamine, ammonium acetate and formaldehyde or a formaldehyde equivalent such as hexamethylenetetraamine in acetic acid at about 80-100 °C yielded imidazole Compound **A3**. The imidazole Compound **A3** was iodinated by deprotonation at the number 2 carbon with a strong base such as lithium

diisopropylamide (LDA) at about -20 to about -78 °C followed by addition of iodine to give the iodinated imidazole Compound **A4**. Compound **A4** was then coupled with a compound of the formula $-\text{CC}(\text{Y})\text{Cl}$; wherein Y is as defined herein, using a palladium (II) [Pd(II)] catalyst such as tetrakis

- 5 tris(triphenylphosphine) palladium (II) in acetonitrile and excess triethylamine at 80 °C for 3-18 hours to obtain the intermediate Compound of **Formula II**. The Compound of **Formula II** was reacted with excess alkylamine $\text{H}_2\text{N}(\text{W})$ in methanol at about 70 °C to about 80 °C for about 3 to about 18 hours (h) and resulted in a secondary amine intermediate which was then subjected to an
- 10 intramolecular Michael addition to obtain the target Compound of **Formula I**.

Scheme A



- 15 Compounds of **Formula I** may be used in pharmaceutical compositions to treat patients (humans and other primates) with disorders related to the overproduction of inflammatory cytokines, particularly $\text{TNF-}\alpha$. The preferred route is oral administration, however compounds may be administered by intravenous infusion or topical administration. Oral doses range from about
- 20 0.01 to 100 mg/kg, daily. Some compounds of the invention may be orally

dosed in the range of about 0.01 to about 50 mg/kg daily, while others may be dosed at 0.01 to about 20 mg/kg daily. Infusion doses can range from about 1.0 to 1.0×10^4 $\mu\text{g/kg/min}$ of inhibitor, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days. For topical administration compounds of Formula I may be mixed with a pharmaceutical carrier at a concentration of about 0.1 % to about 10% of drug to vehicle.

The novel compounds of Formula I and pharmaceutical compositions thereof of this invention inhibit the in vitro activity of p-38 in the nanomolar range. In addition, the compounds and pharmaceutical compositions thereof inhibit the in vitro secretion of TNF- α and IL-1 β in the nanomolar range. Animal models demonstrate the inhibition of LPS induced TNF- α , as well as the inhibition of rheumatoid arthritis.

With this range of activity, the compounds and associated pharmaceutical compositions of the invention are useful in the treatment of a variety of cytokine related disorders including, but no limited to, rheumatoid arthritis, inflammatory bowel disease, septic shock osteoporosis, osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin dependent diabetes, periodontal disease, restenosis, alopecia areta, T-cell depletion in HIV infection or AIDS, psoriasis, acute pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, multiple sclerosis, cachexia, Alzheimer's disease, stroke, Crohn's disease, inflammatory bowel disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus.

Pharmaceutical compositions of the present invention can be prepared using conventional pharmaceutical excipients and compounding techniques. Oral dosage forms may be elixirs, syrups, capsules tablets and the like. Where the typical solid carrier is an inert substance such as lactose, starch, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, mannitol and the like; and typical liquid oral excipients include ethanol, glycerol, water and the

like. All excipients may be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known to those skilled in the art of preparing dosage forms.

5 Parenteral dosage forms may be prepared using water or another sterile carrier.

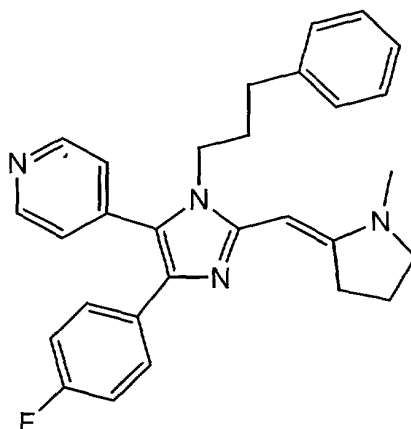
Typically the compounds of Formula I are isolated and used as free bases, however the compounds may be isolated and used as their pharmaceutically acceptable salts. Examples of such salts include
 10 hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartatic, citric, benzoic, mandelic, methanesulfonic, hydroethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic and saccharic.

15 In order to illustrate the invention the following examples are included. These examples do not limit the invention. They are only meant to suggest a method of practicing the invention. Those skilled in the art may find other methods of practicing the invention, which are readily apparent to them. However those methods are deemed to be within the scope of this invention.

20

SYNTHETIC EXAMPLES

Example 1



25 4-[4-(4-fluorophenyl)-2-[(E)-(1-methyl-2-pyrrolidinylidene)methyl]-1-(3-phenylpropyl)-1H-imidazol-5-yl]-pyridine (Compound 1)

The starting material for Compound 1 was prepared as illustrated by the procedure used for Compound 14, found in U.S. Patent 5,965,583. Compound 14 (1.39 grams, 3.04 mmol) was placed in a tube and a 2N solution of methylamine (15 mL) and 4-dimethylaminopyridine (5 mol%) was added. The tube was sealed and placed in an oil bath heated to about 70°C for about 24 h. The tube was removed from the oil bath and allowed to cool to ambient temperature before being opened. The mixture was evaporated in vacuo and the crude product was purified by column chromatography (silica gel) using a mobile phase consisting of methylene chloride:methanol in a 19:1 (v/v) ratio and afforded Compound 1 which was recrystallized from ethyl acetate-hexane; m.p. 171-172°C; MS 453 (MH⁺). ¹H NMR (CDCl₃) δ 8.59 (d, 2H) 4.52 (s, 1H, exch.), 2.75 (s, 3H, CH₃).

Example 2

4-[4-(4-fluorophenyl)-2-[(E)-(1-ethyl-2-pyrrolidinylidene)methyl]-1-(3-phenylpropyl)-1H-imidazol-5-yl]-pyridine (Compound 2)

Following the procedure of Example 1 and substituting the appropriate starting materials, compounds and reagents, Compound 2 was also prepared; m.p. 126.6-127.6°C; MS 467 (MH⁺).

BIOLOGICAL EXAMPLES

As discussed previously, agents which inhibit the activity of the enzyme p38, inhibit the production of the inflammatory cytokines TNF-α and IL-1. The biological activity of the compounds of the present invention was demonstrated by in vitro and in vivo assays.

Example 3

Compounds of the invention were measured for their ability to inhibit the activity of p38 in an in vitro whole cell assay using peripheral blood mononuclear cells ("PBMC") obtained from human blood as follows. Freshly obtained venous blood was anticoagulated with heparin, diluted with an equal volume of phosphate buffered saline ("PBS") and placed in a sterile tube or other container. Aliquots (30 mL) of this mixture were transferred to centrifuge tubes which were underlaid with Ficoll-Hypaque (15 mL). The prepared tubes

were centrifuged at 400 x g without braking for 30 min at room temperature. Approximately 1/2 to 2/3 of the platelet layer above the mononuclear cell band was removed with a pipet. The majority of the mononuclear cell layer was carefully removed using a pipet and these PBMCs were diluted with PBS and spun at 600 x g for 15 min. The resulting PBMCs were washed with another portion of PBS and spun at 400 x g for 10 min at room temperature. The recovered pellets were diluted in low endotoxin RPMI / 1% FCS culture medium and gave a cell concentration of 0.5-2.0 X 10⁶ PMBC/ mL. A small volume of the suspension was removed for counting on a hemocytometer and the remaining preparation was centrifuged at 200 x g for 15 min at room temperature. The recovered pelleted PMBC were resuspended in RPMI / 1% FCS to a concentration of 1.67 x 10⁶/mL.

To run the assay, the PBMC suspension (180 µL) was transferred to duplicate wells of a 96-well flat-bottom microtiter plate and incubated for 1h at 37 °C. A solution of test compound (10 µL: prepared at 20 x the desired final concentration) was added to each well and the plate was incubated for 1 h at 37 °C. A solution (10 µL) of LPS in RPMI / 1% FCS (200 ng/mL) was added and the wells were incubated overnight at 37 °C. The supernate (100 µL) was removed from each well and diluted with RPMI / 1% FCS (400 µL). The samples were analyzed for TNF-α using a commercial ELISA kit (Genzyme), resulting in data as shown in Table A.

Example 4

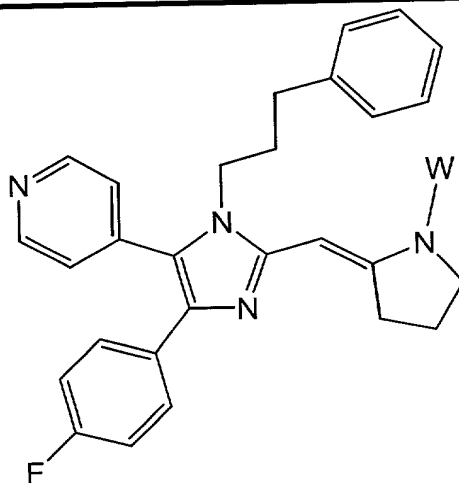
The ability of the compounds of Formula I to inhibit LPS induced TNF-α production was demonstrated in the following in vivo rodent assay. Mice (BALB / cJ females, Jackson Laboratories) or rats (Lewis males, Charles River) were fasted for 30 min prior to oral dosing with 5-10 mL/kg of test compound at 5-50 mg/kg. Thirty minutes after dosing, the animals were injected intraperitoneally with LPS at 1 mg/kg and returned to their cages for 1 h. Animals were anesthetized by CO₂, exsanguinated by cardiac puncture and whole blood collected (0.1-0.7 mL). The blood was allowed to clot and serum was transferred to a centrifuge tube. This sample was centrifuged, serum was

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collected, aliquoted and frozen at -80 C. Samples were tested by commercial ELISAs for TNF- α (Endogen for mouse TNF- α and Biosource for rat TNF- α), resulting in data as shown in Table A.

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T02T01 66E8660

TABLE A



Cpd	W	TNF- α IC ₅₀ (nM)	% Inhibition Mouse TNF- α	
			25 mg/kg	10 mg/kg
1	methyl	15	99	77
2	ethyl	17	98	89